CENTER FOR DRUG EVALUATION AND RESEARCH

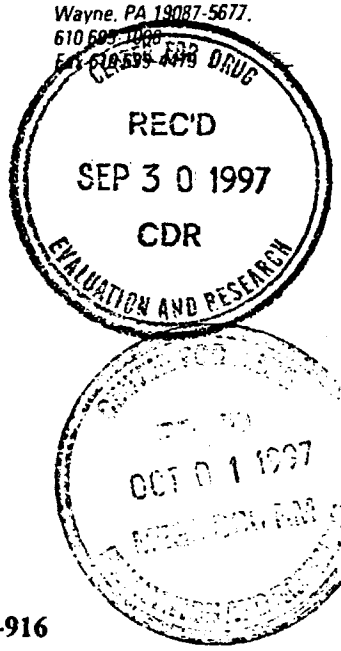
APPLICATION NUMBER: 020916

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

prazole + Amoxicillin + Clarithromycin
Drug Application

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK
725 Chesterbrook Blvd
Wayne, PA 19087-5677
610 695-7000
Fax 610 695-4479



September 30, 1997

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

ORIGINAL NEW DRUG APPLICATION - NDA 20-916
PRILOSEC® Delayed-Release Capsules
(Omeprazole)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21CFR §314.50 we are submitting, for approval, a Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease.

An active New Drug Application (NDA 19-810) exists under the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) for PRILOSEC® Delayed-Release Capsules. The current approved indications include monotherapy treatment for short-term treatment of active duodenal ulcer, active benign gastric ulcer, erosive esophagitis, poorly responsive symptomatic GERD, and, in combination with clarithromycin, the eradication of *H. pylori* for reduction of the risk of duodenal ulcer recurrence. Also approved are indications for long-term treatment of pathological hypersecretory conditions and to maintain healing of erosive esophagitis.

The present New Drug Application is supported by three adequate and well-controlled trials, two of which were conducted by Astra Merck (Studies 126 and 127) and one study which was conducted by . (Study M96-446). The results of these trials and 4 supportive studies conducted by Astra Merck, Astra Hässle establish the safety and effectiveness of PRILOSEC plus amoxicillin plus clarithromycin in eradicating *H. pylori* and thus reducing the risk of ulcer recurrence in these patients. Moreover, the data summarized herein demonstrate that the regimen

eradicates *H. pylori* in patients who had an ulcer at the initiation of therapy as well as in those who did not have an ulcer at the time of treatment.

In addition to this New Drug Application, a supplement to NDA 19-810 will be submitted to the Division of Gastrointestinal and Coagulation Drug Products. The sNDA will provide for labeling changes describing the claim and supporting data contained in the present NDA. The labeling contained in the sNDA will be identical to that contained in Item 2 of the present submission.

Reference is made to two Pre-NDA meetings with FDA on March 13, 1997 and July 15, 1997 (joint meetings with the Division of Special Pathogens and Immunologic Drug Products and the Division of Gastrointestinal and Coagulation Drug Products). At these meetings agreements were made regarding the format and content of the NDA, which have been incorporated into this application.

We are submitting, under separate cover, statistical data sets in SAS for the three pivotal trials (studies 126, 127 and M96-446) to aid in the statistical review. In addition, as agreed to during the previously mentioned Pre-NDA meetings, electronic data files containing case report form (CRF) data in ASCII format for the pivotal trials will be submitted in lieu of printed paper copies of CRF tabulations (normally submitted as Item 11). Finally, electronic text versions of the Clinical Study Reports for studies 126, 127 and M96-446 will also be provided.

This application is formatted as required in 21CFR §314.50. It consists of an archival copy (Blue Binders) of the entire submission (93 volumes), and review copies of Items 2, 6, 7, 8 and 10 as described in the statement of organization attached to this letter. Reference is made to NDA 19-810 for Items not required for review of this application (Chemistry Manufacturing and Controls Data, Non-Clinical Data, and Human Pharmacokinetics and Bioavailability Data). In addition, as required by 21CFR §314.70(a), a complete field copy of Items 3 and 4 (Environmental Assessment and Labeling) of this NDA is being submitted simultaneously to the FDA Philadelphia District Office.

In accordance with the Prescription Drug User Fee Act of 1992, a check in the amount of (Check No.) was sent to the Food and Drug Administration, Pittsburgh, PA, on September 19, 1997 (User Fee I. D.) in support of this application. (See attached letter and FDA Form 3397.)

As required by Section 306(k)(l) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(l)], we hereby certify that, in connection with this application, Astra Merck Inc. did not and will not use in any capacity the services of any person debarred under subsection 309 (a) or (b) of the Act.

We consider the filing of this New Drug Application to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Desk Copy (Letter Only): Dr. L. Talarico, Acting Director (HFD-180)

Desk Copy (Cover Letter and Items 3 and 4): Philadelphia District Office
Federal Express No.:4370470941

Hand Deliver

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA ACKNOWLEDGEMENT LETTER

Food and Drug Administration
Rockville MD 20857

NDA 20-916

Attention: Gary Horowitz, Ph.D.
Astra Merck Inc.
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

Dear Dr. Horowitz:

We have received your new drug application (NDA) submitted under section 505(b)/507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Prilosec (Omeprazole) Delayed Release Capsules 20 mg

Therapeutic Class: 6S

Date of Application: 9-30-97

Date of Receipt: 9-30-97

Our Reference Number: NDA 20-916

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)/507 of the Act on in accordance with 21 CFR 314.101(a).

Should you have any questions, please call: Robin Anderson
Project Manager
(301) 827-2335

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Pauline Fogarty
Acting Chief, Project Management Staff
Division of Special Pathogens and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: NDA 20-916
HFD-590/Div. File
MO-Hopkins
Pharm:Hundley
Chem: Holbert
Micro: Utrup
Biopharm: Ajayi
Stat: Silliman
CSO: Anderson

MARJORIE H. CHRISTIE, Ph.D.
Director, Regulatory Operations

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1925
Fax 610 889-1291

September 19, 1997

Dr. Mark Goldberger, Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Goldberger,

Attached please find copy of User Fee letter that was sent on this day; September 19,1997 to ., along with a check in the amount of in support of PRILOSEC® Type 6 New Drug Application 20-916 for your records.

Sincerely yours,

Marjorie Christie

Marjorie H. Christie, Ph.D.
Director, Regulatory Operations

MARJORIE H. CHRISTIE, Ph.D.
Director, Regulatory Operations

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1925
Fax 610 889-1291

Sept. 19, 1997

Food and Drug Administration
PO Box 360909
Pittsburgh, PA 15251-6909

RE: NDA 20-916: PRILOSEC® (omperazole) Delayed Release Capsules
User Fee I.D. Number:

In accordance with the Prescription Drug User Fee Act of 1992, a check in the amount of (Check No.) is being sent to the Food and Drug Administration, in support of the PRILOSEC® Type 6 New Drug Application for the use of omeprazole plus amoxicillin plus clarithromycin in the treatment of *Helicobacter pylori* .

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application Astra Merck Inc. did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.

We consider the fact of filing this New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Questions regarding this application should be directed to Gary Horowitz, Ph.D., Director, Regulatory Liaison, (610/695-1008) or, in his absence, Barbara Blandin, Regulatory Project Manager, (610/695-1540).

Sincerely yours,

Marjorie Christie

Marjorie H. Christie, Ph.D.
Director, Regulatory Operations

FedEx Tracking Number:

Enclosure (Check No.),
cc: Ms. Robin Anderson, Project Manager Special Pathogens
Dr. Mark Goldberger, Acting Director

ELLIOTT T. BERGER, Ph.D
Executive Director, Regulatory Affairs

ASTRA MERCK

725 Chesterbrook Blvd
Wayne, PA 19087-5677
610 695-1057
Fax 610 889-1292

March 3, 1997

VIA FEDEX

Stephen B. Fredd, M.D. - Director
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180 Room 6B-45
Office of Drug Evaluation
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Fredd:

NDA 19-810: PRILOSEC® Delayed Release Capsules
(Omeprazole) - Update to Patent Information
TIME SENSITIVE PATENT INFORMATION

Enclosed please find the original and one copy for each of the following:

(1) new patent information for U.S. Patent No. 4,636,499 ("'499 patent");

(2) new patent information for U.S. Patent No. 5,093,342 ("'342 patent");

and

(3) new patent information for U.S. Patent No. 5,599,794 ("'794 patent").

In addition, pursuant to 21 CFR § 314.53, we also enclose Declarations for the '342 and '794 patents that cover methods of use (original and copy for each), as set forth in the Declaration for each patent.

APPEARS THIS WAY
ON ORIGINAL

Astra Merck Inc. respectfully requests that the FDA update its records and include the '499, '342 and '794 patents in the publication, Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") in accordance with this letter and enclosures.

Questions regarding this submission should be forwarded to Elliott T. Berger, Ph.D. (610/695-1057).

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Elliott T. Berger, Ph.D.
Executive Director
Regulatory Affairs
Astra Merck Inc.

FedEx No. _____

Enclosures

cc: Drug Information Services Branch
HFD-84
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Via FedEx (w/enclosures)
FedEx No. _____

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION FOR OMEPRAZOLE (PRILOSEC®) - APPLICATION NUMBER 19810 001

1. Applicant	Astra Merck Inc.
2. Patent No. Expiration Date	4,636,499 May 30, 2005
3. Type of Patent	Drug substance
4. Name of the Patent Owner	Aktiebolaget Hässle
5. Representative authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 314.52 and 314.95	Astra Merck Inc.

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION FOR OMEPRAZOLE (PRILOSEC®) - APPLICATION NUMBER 19810 001

1. Applicant	Astra Merck Inc.
2. Patent No. Expiration Date	5,093,342 February 2, 2010
3. Type of Patent	Method of use
4. Name of the Patent Owner	Aktiebolaget Hässle
5. Representative authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 314.52 and 314.95	Astra Merck Inc.

APPEARS THIS WAY
ON ORIGINAL

DECLARATION

The undersigned declares that Patent No. 5,093,342 covers a method of use of omeprazole (PRILOSEC®), i.e., treatment of H. pylori-associated Duodenal Ulcer. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act: Application No. 19810 001.

Elliott T. Berger, Ph.D.
Executive Director,
Regulatory Affairs
Astra Merck Inc.

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION FOR OMEPRAZOLE (PRILOSEC®) - APPLICATION NUMBER 19810 001

1. Applicant	Astra Merck Inc.
2. Patent No. Expiration Date	5,599,794 February 4, 2014
3. Type of Patent	Drug product and method of use
4. Name of the Patent Owner	Astra Aktiebolag
5. Representative authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 314.52 and 314.95	Astra Merck Inc.

APPEARS THIS WAY
ON ORIGINAL

DECLARATION

The undersigned declares that Patent No. 5,599,794 covers the formulation, composition, and method of use of omeprazole (PRILOSEC®), i.e., H. pylori-associated Duodenal Ulcer. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act: Application No. 19810 001.

Elliott T. Berger, Ph.D.
Executive Director,
Regulatory Affairs
Astra Merck Inc.

APPEARS THIS WAY
ON ORIGINAL

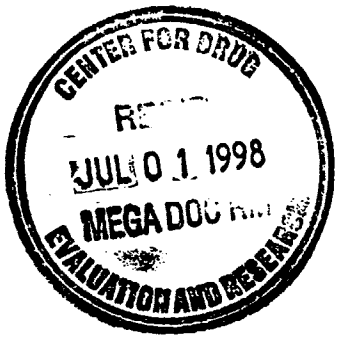
GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

June 29, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR
INFORMATION - AMENDMENT TO PENDING APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to our submission of final draft labeling on June 25, 1998, and to a fax sent to us by the Agency on June 29, 1998.

With this letter we are submitting revised draft labeling for PRILOSEC® which incorporates the Agency request of June 29, 1998. In addition, please note one additional editorial change on page 14 line 2: the term γ-glutamyl had been incorrectly printed as g-glutamyl on the June 25, 1998 version. This error has been corrected on the attached final draft labeling.

We consider the filing of this amendment to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

As requested, we are also providing an electronic copy of the revised draft labeling in MS Word 7.0 on a 3½" diskette.

Please direct any questions or requests for additional information to me at (610)-695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager (610)-695-1540.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Barbara J. Blandin for
Gary P. Horowitz, Ph.D.
Director, Regulatory Liaison

Attachment

Federal Express No.: 805677199591

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-916 SUPPL #_____

Trade Name PRILOSEC Generic Name omeprazole

Applicant Name Astra Merck HFD-590

Approval Date 6/29/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X__/

If yes, NDA #_____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X__/

If your have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /__X_/
Investigation #2	YES /___/	NO /__X_/
Investigation #3	YES /___/	NO /__X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

APPEARS THIS WAY
ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # 126

Investigation #_, Study # 127

Investigation #_, Study # Abbott M96-446

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For eaeh investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /_X_/ NO /___/ Explain: ____

Investigation #2

IND # ____ YES /_X__/ NO /___/ Explain: ____

Investigation #3

IND # ____ YES /_X__/ NO /__X_/ Explain: Abbott study/written for use permission given by Abbott

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #3

YES /__X_/ Explain _____ NO /___/ Explain _____

- Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____

/S/

Robin Andersor, _____ 6/29/98
Signature Date

Title: Project Manager

/S/

_____ 7/2/98
Signature of ~~Division~~ Director Date

cc: Original NDA 20-916
HFD-590 Division File
HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-916 Supplement # ___Circle one: SE1 SE2 SE3 SE4 SE5 SE6
HFD-590
Trade and generic names/dosage form: PRILOSEC®, (omeprazole) 20 mg, in combination with amoxicillin 1000mg and clarithromycin 500mg
Action: AP AE NA
Applicant Astra Merck Therapeutic Class H.pylori
Indication(s) previously approved: duodenal ulcer
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate___

Indication in this application: Eradication of *Helicobacter pylori* in patients with duodenal ulcer disease

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

XX 5. **If none of the above apply,** attach an explanation, as necessary. **Safety and effectiveness in pediatric patients have not been established.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Signature of Preparer and Title
Robin Anderson, Project Mananger

Date
June 29, 1998

cc: Orig NDA/PLA/PMA # 20-916
HFD-590/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 7/1/98)

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

ORIGINAL

January 30, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
SAFETY UPDATE REPORT

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to my telephone and fax communications with Robin Anderson on November 21, 1997 regarding our proposed format for the required Safety Update Report.

With this letter we are submitting ITEM 9: Safety Update Report for this NDA, as required by 21CFR 314.50 and in accordance with the agreements made in the referenced communications. This report contains clinical safety information from five completed clinical trials which became available to Astra Merck after the original NDA was submitted. Four of the studies were conducted by Astra Hässle, and one study was conducted by Astra Merck. In addition, this report contains an update of information on serious adverse events both reported in clinical trials and obtained through post-marketing surveillance during the period between March 31, 1997 and September 30, 1997.

One of the four clinical study reports obtained from Astra Hässle (Astra Hässle Study SH-OMH-0016) summarizes a drug interaction study conducted in healthy volunteers receiving omeprazole, clarithromycin and amoxicillin concomitantly. The results of this study will also be submitted under separate cover to support a revision to the proposed draft labeling that was submitted in the original NDA.

We consider the filing of this Safety Update Report to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Gary P. Horowitz

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

APPEARS THIS WAY
ON ORIGINAL

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

NC
NEW CORRESP
DUPLICATE

December 5, 1997

Mark Goldberger, M.D., Acting Director
Division of Special Pathogen and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules (Omeprazole)

Please refer to our Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules (omeprazole), clarithromycin, and amoxicillin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted on September 30, 1997. Please also refer to my interactions on November 21, 1997 with Nancy Sager, Team Leader of the Environmental Assessment Team regarding the Environmental Assessment (EA) included in the NDA. Ms. Sager requested information on whether there are differences between the EA submitted to NDA 20-754 (omeprazole plus amoxicillin for eradication of *H. pylori*; now withdrawn) and the EA for NDA 20-916. With this letter we are providing that information.

There are three areas of differences between the EA for NDA 20-754 (omeprazole plus amoxicillin) and the EA for NDA 20-916 (omeprazole plus amoxicillin plus clarithromycin).

1. Based on updated production forecasts, the expected introduction concentration (EIC) calculation in the EA for NDA 20-916 the threshold, requiring that information contained in Sections 7 through 11 of the EA be completed. The calculated EIC for the EA in NDA 20-916 was (based on total U.S. PRILOSEC forecast, 5th year anticipated post-approval). The calculated EIC for the EA in NDA 20-754 was (based on total U.S. PRILOSEC forecast, 5th year anticipated post-approval.

2. The EA for NDA 20-916 identifies two alternate in addition to the other facilities listed in the EA for NDA 20-754.

3. The EA for NDA 20-916 contains some updated environmental information on the manufacturers (i.e. Sections 4 and 6 re: permit limits, permit expiration dates etc.) compared to the information contained in the EA for NDA 20-754.

Please direct any questions or requests for additional information to me at 610/695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

FedEx No.:

Desk Copy: Ms. Nancy Sager, HFD - 357
FedEx No.:

Philadelphia District Office
FedEx No.:

APPEARS THIS WAY
ON ORIGINAL

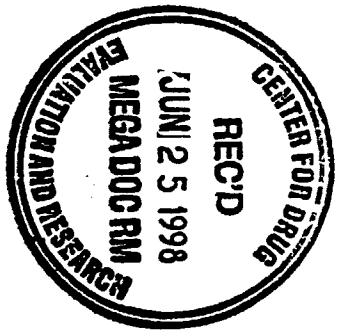
GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

BL

DUPLICATE



June 25, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR
INFORMATION - AMENDMENT TO PENDING APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to a fax sent to us by the Agency on June 17, 1998 providing labeling recommendations for the indication, the subsequent teleconference with the Agency on June 19, 1998, to discuss these recommendations, and an additional fax sent by Dr. Silliman, Statistical Reviewer, on June 24, 1998.

With this letter we are submitting revised draft labeling for PRILOSEC® which incorporates the Agency recommendations of June 19 and June 24, 1998. In order to maintain consistency, we have made some editorial changes to the text that was provided in the Agency recommendations. A summary of these editorial changes is provided with the draft labeling.

In addition, please note that the original draft labeling submitted in NDA 20-916 was based on the current approved labeling for PRILOSEC® at that time (package insert no. 7910924). The revised draft labeling being submitted with this letter is based on the current approved labeling at the present time (package insert no. 7910927). The changes to the current approved labeling since the submission of NDA 20-916 include the addition of a 40 mg dosage strength under the DESCRIPTION and HOW SUPPLIED sections, as well as changes to the CLINICAL PHARMACOLOGY, *Enterochromaffin-like (ECL) Cell Effects* subsection.

As requested, we are also providing an electronic copy of the revised draft labeling in MS Word 7.0 on a 3½" diskette.

The attached information is also being submitted simultaneously to NDA 19-810/S-055 under the Division of Gastrointestinal and Coagulation Drug Products.

We consider the filing of this amendment to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610)-695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager (610)-695-1540.

Sincerely yours,

Barbara J. Blandin for

Gary P. Horowitz, Ph.D.
Director, Regulatory Liaison

Attachment

Hand Delivered

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
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DRUG AMENDMENT

DUPLICATE

June 17, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR
INFORMATION - AMENDMENT TO PENDING APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to a teleconference with the Agency on April 1, 1998, to discuss requests for information from the Biopharmaceutics Reviewer, and to the subsequent submission on April 9, 1998, which contained a partial response to those requests.

With this letter we are submitting additional information in response to the Biopharmaceutics Reviewer's requests. The documents that are enclosed are listed below.

Information Enclosed:

Formulation Composition	Quantitative formulation composition for the study drugs used in the Astra Studies I-1221, I-1238 and SH-OMH-0016.
Certificates of Analysis	Certificates of Analysis for the study drugs used in the Astra Studies I-1221, I-1238 and SH-OMH-0016.

In a telefacsimile sent to Ms. Robin Anderson on 16 June 1998, we reported that Analytical Validation Reports for amoxicillin determination in Studies I-1214 and I-1221 would be provided herein. Please note that these reports have already been provided to you. The outstanding reports should be noted as omeprazole determination; these latter reports are still not available.

We have been informed by Astra Hässle that *in vitro* dissolution profiles are not currently available for drugs used in Astra Studies I-1221, I-1238 and SH-OMH-0016. In addition, neither formulation composition nor *in vitro* dissolution profiles are available for the study drugs used in Study I-1214.

We consider the filing of this amendment to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610)-695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager (610)-695-1540.

Sincerely yours,

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

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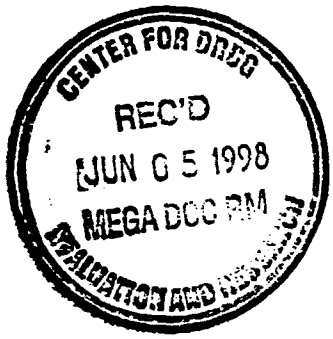
BL

ORIG AMENDMENT

ORIGINAL

June 4, 1998



Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR
INFORMATION - AMENDMENT TO PENDING APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to a telephone call I received from Ms. Robin Anderson on June 4, 1998 at which time she requested the Proposed Text of Labeling for the NDA in electronic format (MS Word 7.0).

With this letter we are providing the Proposed Text of Labeling (unannotated) in MS Word 7.0 on a 3½" diskette (2 copies) as well as a hard copy of the file contained on the diskette.

We consider the filing of this information to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610)-695-1008 or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610)-695-1540.

Sincerely yours,

Gary P. Horowitz

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy: Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
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NC
NEW CORRESP
ORIGINAL

May 21, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997.

On May 20, 1998, we received a fax from the Agency with two questions from Dr. Silliman, the Statistical Reviewer for this NDA. With this letter we are responding to Dr. Silliman's questions.

Question 1: **For Studies 126 and 127, the applicant states that "patients were analyzed according to the study treatment that was actually given to the patient to take". This was for both the per-protocol and intent-to-treat analyses. Were there actually any patients randomized to one treatment arm who ended up receiving the other treatment? If so, how many in each treatment arm/analysis population/study?**

Answer: The clinical study reports for Studies 126 and 127 states the following in Section 5.7.1.2.1 Data Handling Conventions, Efficacy: "For both patient populations, patients were analyzed according to the study treatment that was actually given to the patient to take." This was stated in the reports to account for the possibility that study medication might have been accidentally switched at the investigator sites. However, in Studies 126 and 127, all patients were given the correct study medication according to the randomized allocation number that they received. There were no

and 127, all patients were given the correct study medication according to the randomized allocation number that they received. There were no patients who were randomized to one treatment arm, but ended up receiving the other treatment arm in either of these two studies. Thus, all patients were analyzed according to the study medication that they were (correctly) given to take according to the random allocation schedule.

Question 2: **There appear to be patients in the per-protocol analyses who are missing *H. pylori* eradication information at Week 8. For example, in the triple therapy arm of Study 127 there are 5 smokers who are "in the per-protocol analysis" but actually aren't because there is no *H. pylori* information on them at follow-up. Didn't patients have to have data at the follow-up to be included in the per-protocol group?**

Answer: Patients were considered to be evaluable and were included in the per-protocol analysis as long as they did not violate several prespecified criteria. One such criteria (Criteria G.) states that "patient returned for the final endoscopy office visit and had efficacy measures taken." To identify patients who violated this particular criteria, patients who did not have at least one post-baseline endoscopy performed on or after Study Day 2 and did not have some efficacy measures taken (either the determination of the presence/absence of a duodenal ulcer or results for the CLOtest®) were identified and excluded from the per-protocol analysis.

The primary efficacy endpoint for these studies was *H. pylori* eradication at Week 8 (the targeted final endoscopy timepoint). A day range was determined for *H. pylori* eradication at Week 8. In order to classify a patient as having *H. pylori* eradicated at the Week 8 timepoint, the *H. pylori* status must be determined to be negative on or after Study Day 53, where Study Day 1 is the first day that study medication was taken by a patient. *H. pylori* status was determined to be negative at Week 8 if none of the three diagnostic tests (CLOtest®, histology or culture) was positive and if at least two of these tests were negative for *H. pylori*. However, if the *H. pylori* status at Week 8 was not determined to be negative and if the *H. pylori* status was considered to be positive (at least one diagnostic test showed positive results for *H. pylori*) on or after Study Day 29 (the first day after the end of the 28 days on therapy), the patient was considered to still be infected with *H. pylori* at the Week 8 timepoint. This very conservative approach assumes that if after finishing the prescribed treatment regimen of 10 days of *H. pylori* eradication therapy plus an additional 18 days of omeprazole for ulcer healing and symptom relief, *H. pylori* has not been eradicated, then *H. pylori* will not be eradicated

spontaneously throughout the remainder of the study while the patient is not on treatment.

As an example, consider a hypothetical patient who had an endoscopy performed and was considered to be *H. pylori* infected at baseline. Suppose this patient took study medication throughout Days 1-28, and had one more endoscopy performed on Study Day 30 which revealed a positive CLOtest®, negative culture and negative histology results. If no later endoscopy was performed, the patient would be considered to be still infected with *H. pylori* (ie., *H. pylori* not eradicated) at the Week 8 timepoint. This patient would be included in the per-protocol analysis as a failure for *H. pylori* eradication.

Table 7 in the clinical study reports for both Studies 126 and 127 outlines the day ranges used for both the baseline and Week 8 targeted endoscopy timepoints.

We are not sure exactly which 5 patients in Study 127 Dr. Silliman is identifying for this question. If Dr. Silliman would like us to address those 5 patients specifically, perhaps you could send us the allocation numbers of those patients if the above explanation does not address the question.

We consider the filing of this information to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

BM

ORIG AMENDMENT

ORIGINAL

April 22, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR
INFORMATION - AMENDMENT TO PENDING APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to a telephone call I received from Dr. Robert Hopkins on April 16, 1998 at which time he requested additional information regarding ; Study No. M96-446 which was submitted in the NDA.

Dr. Hopkins made the following requests regarding Abbott Study No. M96-446:

1. Recalculate the *H. pylori* eradication rates (counts and proportions), by treatment group, for the following classifications using the per-protocol approach:

   a) Patients with a history of DU disease within 5 years of entering the study

   b) Patients with a history of DU disease between 5 and 6 years prior to entering the study

   c) Patients with a history of DU disease longer than 6 years prior to entering the study, noting any patients who would have been excluded from the per-protocol analysis for reason(s) other than inadequate ulcer history.

2. From Form 1, Page 1 of the Case Report Form (Section Criteria Checklist, Inclusion Criteria), supply the total numbers of patients for each type of source documentation for history of DU disease.

3. Supply copies of completed Case Report Forms (Form 1, Page 1 only) for each of the 24 patients with a history of documented DU disease longer than 5 years prior to entering the study (as described in Table 6.2a of the Clinical Study Report for Study M96-446).

With this letter we are providing responses to Dr. Hopkins' requests detailed above, which were prepared by Abbott Laboratories personnel.

We consider the filing of this information to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
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ORIG AMENDMENT
BZ

DUPLICATE

April 9, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
RESPONSE TO FDA REQUEST FOR
INFORMATION - AMENDMENT TO PENDING APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to a memo received via telefacsimile on March 27, 1998, and the teleconference that followed on April 1, 1998, to discuss requests for information from the Biopharmaceutics Reviewer.

The Biopharmaceutics Reviewer indicated that there were apparent discrepancies in some information presented in Astra Study SH-OMH-0016, and requested that these be resolved and a revised report issued. In addition, she requested quantitative formulation composition, *in vitro* dissolution profiles for all study drug, and quality control/validation data during the analysis of plasma samples for Astra Studies I-1214, I-1221, I-1238 and SH-OMH-0016. Dr. Hopkins also made a request for any data comparing the LOSEC® formulation marketed in Europe with the PRILOSEC® formulation marketed in the U.S.

With this letter we are submitting a partial response to the above requests. The documents that are enclosed are listed below. In addition, we are providing a list of the information not available at this time that will provide the balance of the response, along with an estimate for when it will be available.

Information Enclosed:

Astra Study SH-OMH-0016:	Revised pages for the Clinical Study Report (page 7) and the Clinical Study Synopsis. Four Separate Bioanalytical Study Validation Reports for the determination of 1) omeprazole; 2) omeprazole sulfone, H 168/66, and hydroxy-omeprazole, H 195/80; 3) amoxicillin; and 4) clarithromycin and 14-OH-Clarithromycin in plasma samples for Study SH-OMH-0016
Astra Study I-1214:	Bioanalytical Study Validation Report for the determination of amoxicillin in plasma samples for Study I-1214
Astra Study I-1221:	Three Separate Bioanalytical Study Validation Reports for the determination of 1) amoxicillin; 2) erythromycin; and 3) roxithromycin in plasma samples for Study I-1221
Astra Study I-1238:	Two Separate Bioanalytical Study Validation Reports for the determination of 1) omeprazole and 2) amoxicillin in plasma samples for Study I-1238

Information Not Available (*to be submitted within the next week*):

Astra Study I-1214:	Bioanalytical Study Validation Report for the determination of omeprazole in plasma samples for Study I-1214
Astra Study I-1221:	Bioanalytical Study Validation Report for the determination of omeprazole in plasma samples for Study I-1221
In vitro Dissolution Data	Dissolution profiles for the study drugs used in the Astra Studies I-1214, I-1221, I-1238 and SH-OMH-0016.
Formulation Composition	Quantitative formulation composition for all of the study drugs used in the Astra Studies I-1214, I-1221, I-1238 and SH-OMH-0016.

Information Not Available (*to be submitted within the next 2 weeks*):

Comparison Data for LOSEC® and PRILOSEC®:	Available information is being gathered and will be submitted within the next 2 weeks.

We consider the filing of this amendment to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Barbara J. Blandin for

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

APPEARS THIS WAY
ON ORIGINAL

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

April 3, 1998

ORIGINAL

BM

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
AMENDMENT TO PENDING NEW DRUG APPLICATION

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to our submission of the four-month Safety Update Report (SUR) on January 30, 1998.

The SUR included information regarding the Astra Merck clinical study entitled "A Multicenter, Open-Label, Randomized Study to Compare the Tolerability of Ten Day Omeprazole Triple Therapy to Fourteen Day Bismuth Triple Therapy in Subjects Receiving Treatment for *Helicobacter pylori* Eradication" (Protocol No. 115). At the time of submission of the SUR this clinical trial had been completed; however, the clinical study report was undergoing preparation.

With this letter we are submitting the completed clinical study report for protocol No. 115, which consists of 8 volumes.

We consider the filing of this amendment to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Barbara J. Blandin for

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

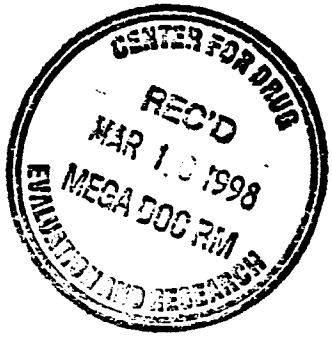
DUPLICATE

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

March 9, 1998



Mark Goldberger, M.D., Acting Director
Division of Special Pathogen and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
GENERAL CORRESPONDENCE

Please refer to our Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules (omeprazole), clarithromycin, and amoxicillin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to FDA on September 30, 1997 and is pending approval.

With this letter we are providing a copy of a letter sent to Khyatie N. Roberts regarding the use of PRILOSEC® in pediatric patients. The letter outlines areas of pediatric clinical need and current deficiencies of information about omeprazole for use in pediatric patients.

Please direct any questions or requests for additional information to me at 610/695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Gary P. Horowitz

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachments

FedEx No.:

NC

NEW CORRESP

ORIGINAL

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Westerbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

February 4, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogen and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

Dear Dr. Goldberger:

ORIGINAL NEW DRUG APPLICATION - NDA 20-916
PRILOSEC® Delayed-Release Capsules
(Omeprazole)
SUBMISSION OF ELECTRONIC TEXT DOCUMENTS

Please refer to our Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules (omeprazole), clarithromycin, and amoxicillin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted on September 30, 1997. In our cover letter accompanying the original submission, we indicated that we would provide, under separate cover, electronic text documents for selected submission documents to aid in the review.

With this letter we are providing two (2) 3 ½" diskettes (1 Reviewer copy and 1 Archival copy) which contain the following documents in Word for Windows 7.0:

1. Clinical Study Reports (excluding appendices) for Astra Merck Studies 126 and 127, and Abbott Laboratories Study M96-446.

2. Integrated Summaries of Efficacy, Safety, and Benefits/Risks.

The files have been compressed using Pkware software, which is included on the diskettes. Attached to this letter is a page containing instructions to expand the compressed files using the Pkware software.

Please direct any questions or requests for additional information to me at 610/695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Barbara J. Blandin for
Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachments

FedEx No.:

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

ORIGINAL

January 30, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)
SAFETY UPDATE REPORT

Reference is made to the Type 6 New Drug Application for the concomitant use of PRILOSEC® Delayed-Release Capsules, amoxicillin and clarithromycin for the eradication of *H. pylori* in patients with duodenal ulcer disease, which was submitted to the Agency on September 30, 1997. Reference is also made to my telephone and fax communications with Robin Anderson on November 21, 1997 regarding our proposed format for the required Safety Update Report.

With this letter we are submitting ITEM 9: Safety Update Report for this NDA, as required by 21CFR 314.50 and in accordance with the agreements made in the referenced communications. This report contains clinical safety information from five completed clinical trials which became available to Astra Merck after the original NDA was submitted. Four of the studies were conducted by Astra Hässle, and one study was conducted by Astra Merck. In addition, this report contains an update of information on serious adverse events both reported in clinical trials and obtained through post-marketing surveillance during the period between March 31, 1997 and September 30, 1997.

One of the four clinical study reports obtained from Astra Hässle (Astra Hässle Study SH-OMH-0016) summarizes a drug interaction study conducted in healthy volunteers receiving omeprazole, clarithromycin and amoxicillin concomitantly. The results of this study will also be submitted under separate cover to support a revision to the proposed draft labeling that was submitted in the original NDA.

We consider the filing of this Safety Update Report to be a confidential matter and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Astra Merck Inc.

Please direct any questions or requests for additional information to me at (610/695-1008) or, in my absence, Barbara J. Blandin, Regulatory Project Manager (610/695-1540).

Sincerely yours,

Gary P. Horowitz

Gary P. Horowitz, Ph.D.
Director, Regulatory Affairs

Attachment

Federal Express No.:

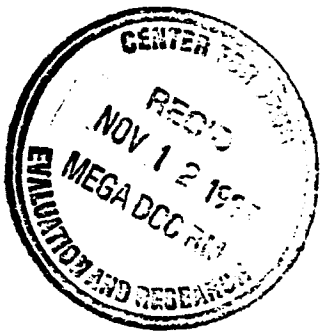
Desk Copy (Letter Only): Dr. L. Talarico, Director (HFD-180)
Federal Express No.:

ORIGINAL NC

GARY P. HOROWITZ, Ph.D.
Director, Regulatory Liaison

ASTRA MERCK
725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1008
Fax 610 695-4479

November 7, 1997



Mark Goldberger, M.D., Acting Director
Division of Special Pathogen and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Goldberger:

NDA 20-916: PRILOSEC® Delayed-Release Capsules
(Omeprazole)

Astra Merck is hereby providing authorization to the Food and Drug Administration to make reference to the efficacy and safety information contained in NDA 20-916 by:

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-3500

By agreeing to allow this reference to our files, we do not, in any way; waive the confidential or trade secret status of the information therein. Furthermore, we do not allow any of the information in our files to be made available to any third party, including Abbott Laboratories, without the prior written consent of Astra Merck Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FASCIMILE CORRESPONDENCE

DATE: March 27, 1998

TO: Gary Horowitz. Director, Regulatory Liaison

ADDRESS: Astra Merck
Fax 610-695-4479

FROM: Mary Dempsey, Project Manager

THROUGH: Houda Mahayni, Ph.D, Reviewing Clin. Pharm. & Biopharmaceutics Officer
Funmilayo Ajayi, Ph.D., Act. Team Leader, Reviewing Clin. Pharm. & Biopharmaceutics Officer

NDA: 20-916

DRUG: Prilosec Delayed-Release Capsules

SUBJECT: Request for information

The Biopharmaceutical reviewers have the following requests:

1. Formulation composition for omeprazole (Losec & Prilosec), Amoxicillin (Imacillin & Amoxil) and Clarithromycin.

2. Quality Control / validation data during the analysis of the plasma samples obtained in study Nos. I-1238, I-1221, I-1214, and SH-OMH-0016.

This NDA is normally handled by Robin Anderson. While Robin is on leave, I will facilitate correspondence between the reviewers and the Company. With this in mind, I will be calling to schedule a telecon next week with the FDA Biopharm reviewers and the Astra Merck counterparts.
Thank you for your cooperation and patience during this interim.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Mary Dempsey
Project Manager
Division of Special Pathogens and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL